槲皮素的药理作用机制及其在奶牛生产中的应用

郭长征　冯泮飞　毛胜勇*

（江苏省消化道营养与动物健康重点实验室，南京农业大学消化道微生物实验室，南京 210095）

摘　要：槲皮素是中草药和果蔬等植物中常见的黄酮醇类物质，具有抗炎、抗菌、抗氧化、抗肿瘤及抗癌等广泛的药理活性。近年来在奶牛研究中发现，槲皮素可改善奶牛瘤胃发酵，对奶牛糖代谢及脂代谢具有一定影响。本文就槲皮素的药理作用机制及其在奶牛生产中的应用进展进行了综述，拟为槲皮素的进一步开发应用提供理论参考。

关键词：槲皮素；生物学作用；机制；奶牛

中图分类号：S816.7；S823

在现代集约化养殖业中，为最大程度地追求生产效益，在奶牛生产中常使用高比例精料[1]；较高的能量摄入及较高的产奶量使奶牛机体氧化代谢增强，进而产生大量活性氧[2-3]，造成机体出现氧化损伤。另外，我国南方夏季炎热高温引发的奶牛热应激问题也常导致动物自身的抗氧化能力下降[4-5]，并对奶牛生产性能、繁殖性能及免疫性能等造成不利影响[6-8]。因此，如何提高动物抗氧化能力已成为当前奶牛生产的一个重要问题。槲皮素（quercetin，3，3’，4’，5，7-五羟基黄酮，图 1）是植物界中分布最广的黄酮类化合物，可减少啮齿动物肝脂肪积聚预防脂肪肝发生[9-10]，同时具有抗氧化、抗炎功能[11-12]。因此，一些研究者认为，开发基于槲皮素为基础的饲料添加剂对保障奶牛健康具有重要意义。本文在前人研究基础上，综述了槲皮素的药理作用机制及在奶牛生产上应用的初步进展，拟为槲皮素的应用开发提供理论参考。

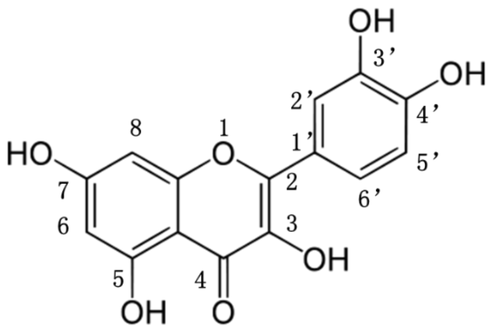

图 1　槲皮素的化学结构

Fig.1　Chemical structure of quercetin[11]

1　槲皮素的药理作用及机制

收稿日期：2016-07-12

基金项目：国家自然科学基金项目(31372339)

作者简介：郭长征(1992-)，男，河南濮阳人，硕士研究生，从事反刍动物营养研究。E-mail: 2014105044@njau.edu.cn

*通信作者：毛胜勇，教授，博士生导师，E-mail:　maoshengyong@163.com

1.1 槲皮素的抗炎作用及机制

研究发现，一些经典的炎性相关疾病如（类）风湿性关节炎、动脉粥样硬化和全身性炎症反应综合征等急慢性炎性疾病的发生或致病过程，均与核转录因子κB（NF-κB）过度或持续激活密切相关[13]。NF-κB 可诱导细胞因子、趋化因子、黏附分子[如细胞间黏附分子-1(ICAM-1)、血管细胞黏附分子-1(VCAM-1)和内皮白细胞黏附分子 1（ELAM1)]大量生成，同时激活一些与炎性级联放大相关的酶[如诱导型一氧化氮合酶(iNOS)和诱导型环氧化合酶]。Cho 等[14]研究表明，槲皮素可抑制细胞外信号调节激酶（ERK）和 p38 丝裂原活化蛋白激酶（p38MAPK）的磷酸化，且通过稳定核转录因子κB/核转录因子κB 抑制蛋白复合体（NF-κB/IκB）阻止核转录因子κB 抑制蛋白(IκB)的脱落，抑制下游白细胞介素-1β（*IL*-1β）、白细胞介素-6(*IL*-6)、肿瘤坏死因子-α（*TNF-α*）及一氧化氮（*NO*）/*iNOS* 的表达。Min 等[15]发现，槲皮素可封阻 p38MAPK 和 NFκB 的活化，减少 *IL*-1β、*IL*-6、*TNF-α*和白细胞介素-8（*IL*-8）的表达。此外，槲皮素可在转录和蛋白质水平抑制前炎症因子诱导 VCAM-1、ICAM-1 和单核细胞趋化蛋白（MCP-1）的表达与合成[16]；抑制激活蛋白-1 的活性和 c-Jun 氨基末端激酶（JNK）通路，减少佛波酯和 TNF-α 诱导人类内皮细胞 ICAM-1 的产生[17]。有研究显示，槲皮素还可抑制 *iNOS* 和环氧化合酶-2(*COX*-2)的表达[18-21]。槲皮素亦可抑制免疫细胞组胺酸脱羧酶的翻译[22]、组胺释放[23]及脱粒[24]。

1.2 槲皮素的抗氧化作用及机制

动物机体在代谢营养物质时，可产生大量自由基，正常情况下，自由基可被体内的防御体系清除；但当机体受损时，自由基可引起细胞薄膜脂质过氧化，导致细胞薄膜损伤，改变渗透压引起细胞肿胀，最终导致细胞死亡[25]。体内自由基的来源包括酶促反应与非酶促反应产生 2 种途径。酶促反应途径中，黄嘌呤氧化酶（XO）、脂氧化酶（LOX）、醛氧化酶（AO）等均为可催化产生自由基的氧化酶；非酶促反应途径是体内某些物质的自动氧化与分子氧的单电子还原途径，自动氧化如过渡金属离子的氧化还原及过氧化物均可产生自由基。目前发现，槲皮素可通过抑制自由基的产生、防止脂质过氧化、激活机体抗氧化体系等方式起到抗氧化作用。

1.2.1 抑制自由基的产生

研究表明，槲皮素可通过抑制黄嘌呤氧化酶活而抑制超氧化物产生[26-27]。Ratty 等[28]用抗坏血酸维生素 C 和硫酸亚铁诱导小鼠脑线粒体脂质过氧化，探究槲皮素的抑制效应，结果表明，槲皮素可同时抑制前述 2 种诱导剂诱导脂质过氧化。

1.2.2 激活机体抗氧化体系

体内的抗氧化酶有超氧化物歧化酶(SOD)、谷胱甘肽过氧化物酶(GSH-Px)和过氧化氢酶(CAT)等。Coskun 等[29]以链脲霉素诱导小鼠糖尿病为模型研究槲皮素添加效应，结果表明，小鼠注射链脲霉素可引起脂质过氧化，显著降低谷胱甘肽过氧化物酶、超氧化物歧化酶、过氧化氢酶活性，而槲皮素则显著提高了上述抗氧化酶的活性。

1.3 槲皮素的抗肿瘤作用及机制

1.3.1　抑制肿瘤细胞增殖

槲皮素对多种恶性肿瘤细胞均有抑制作用，如胃癌细胞（HGC-27、NUGE-2、MKN-7、MKN-28）[30]、结肠癌细胞（COLO320 DM）[30-31]、人乳癌细胞[31-32]、人鳞状细胞和胶质瘤细胞[33-34]、卵巢癌细胞[35]、人肝癌细胞和人胰腺癌细胞[32,36]。肿瘤细胞即使在氧供应充分的条件下，仍以糖酵解方式获取能量，称为有氧糖酵解，这既是著名的“Warburg 效应”。槲皮素抑制肿瘤细胞增殖的原因可能是阻止了肿瘤细胞有氧糖酵解[37]。

1.3.2　诱导肿瘤细胞凋亡

有研究表明，槲皮素可通过激活内部线粒体途径促进肿瘤细胞凋亡。当细胞受到内部凋亡刺激因子作用，凋亡因子 Bax、Bak 等受到激活结合到线粒体外膜，在膜上形成线粒体内部通向胞质的孔道，致使细胞色素 C 等进入细胞质。细胞色素 C 激活凋亡酶激活因子-1（APAF-1），APAF-1 可活化含半胱氨酸的天冬氨酸蛋白水解酶-9（caspase-9）。细胞色素 C、APAF-1、caspase-9 组成凋亡小体，该凋亡小体具有裂解凋亡蛋白酶含半胱氨酸的天冬氨酸蛋白水解酶-7（caspase-7）的作用，caspase-7 裂解激活后引起下游与细胞生命相关蛋白质的降解，最终引起细胞凋亡。B 淋巴细胞瘤-2（Bcl-2）、髓样细胞白血病-1(Mcl-1)、B 淋巴细胞瘤-xL(Bcl-xL)可通过抑制 Bax、Bak 作用，发挥抗凋亡作用[38]。研究表明，槲皮素可下调多种癌细胞 Bcl-2、Mcl-1、Bcl-xL 水平上调 Bax 水平并激活下游通路，促进细胞凋亡，从而起到抗肿瘤作用[39-47]。

1.3.3　抑制肿瘤细胞转移、侵袭

肿瘤侵袭和转移的关键步骤是降解肿瘤周围的基质，基质金属蛋白酶（MMP）能通过破坏基质的降解平衡，进而促进癌细胞突破基底膜和细胞外基质构成的组织学屏障，从而侵袭周围组织和转移至远处组织。有研究表明，槲皮素可通过蛋白激酶 C(PKC)通路下调基质金属蛋白酶前体-9（Pro-MMP-9）[48]；减少 MMP-2、MMP-9 的分泌[32,36]；抑制 MMP-2、MMP-9 的活性[49]，从而抑制癌细胞的侵袭。

2　槲皮素在奶牛生产上的应用进展

2.1　槲皮素的生物利用率

奶牛不同于单胃动物，其瘤胃内栖息着各种微生物，包括瘤胃原虫、瘤胃细菌、和厌氧真菌，还有少数噬菌体[50]。槲皮素是否能够有效进入奶牛外周循环，是其在奶牛上能否发挥出在单胃动物上功能的前提。通过瘤胃瘘管添加槲皮素的动力学试验表明，总黄酮醇（结合与非结合形式槲皮素及结合与非结合形式的槲皮素衍生物之和）的绝对生物利用率仅为 0.1%[51]。有研究表明，槲皮素被瘤胃微生物迅速降解成 3，4-二羟基苯乙酸和 4-甲基邻苯二酚[52]，这可能是生物利用率低的原因。而通过奶牛十二指肠添加槲皮素接近猪等单胃动物口服添加下的生物利用率[53]。因此，过瘤胃添加槲皮素更能发挥其在奶牛生产中的作用。

2.2　槲皮素对瘤胃发酵的影响

槲皮素对变异链球菌、血链球菌、嗜酸乳杆菌和远缘链球菌有抑制效应[54]，暗示其可能通过改变瘤胃微生物菌群从而调控瘤胃发酵。瘤胃是反刍动物消化代谢和营养物质吸收最

重要的场所，饲粮中碳水化合物在瘤胃内被瘤胃微生物发酵产生挥发性脂肪酸（VFA），VFA可为宿主提供60%~80%的能量[55]。瘤胃发酵体外模拟试验表明，添加不同剂量槲皮素瘤胃发酵参数不一致。添加 500 mg/L 槲皮素可显著增加总挥发性脂肪酸（TVFA）浓度[56]，作者认为槲皮素刺激了瘤胃发酵。其他研究表明，添加量为4.5%底物时，槲皮素对pH、TVFA浓度、单一VFA比例无显著影响[57]；槲皮素对干物质降解率及羧甲基纤维素酶、木聚糖酶、β-葡萄糖苷酶活性无显著影响，说明槲皮素并不能改变瘤胃对营养物质的发酵程度[57]；另外，最近的研究表明，槲皮素可被瘤胃微生物迅速降解，通过奶牛瘤胃瘘管添加 50 mg/kg BW的槲皮素对TVFA浓度及各单一VFA比例也无显著影响[52]。此外，与体外发酵相比，瘤胃添加槲皮素被快速吸收入血液或降解；而体外发酵槲皮素不能向肠道外流。因此，部分研究中添加槲皮素显著增加TVFA浓度的结果，可能是槲皮素被瘤胃微生物降解利用造成的。

有研究认为，对于减少甲烷产生，植物次级代谢物相比于离子载体和益生菌具有价格低廉及环保的优势[58]，具有作为抑制甲烷产生的添加剂的潜力，槲皮素是其中分布最广的类黄酮[59]。目前体外发酵试验表明，槲皮素添加量为4.5%底物时，可增加产气量，减少甲烷产量，降低原虫、产甲烷菌数量[57]；培养基中添加 100 μmol/L 的槲皮素对产气量及甲烷产量无显著影响[52]。结果不一可能是试验条件及添加量不同所致。Leiber 等[60]研究发现，添加芦丁（5 和 500 μmol/L 的槲皮素）可显著增加产气量，但是其中甲烷比例下降，作者认为芦丁被非产甲烷微生物作为底物产生 CO_2，从而降低了总产气中甲烷的比例。综上，槲皮素对于产气量和甲烷含量的影响及机制还需进一步研究确定；槲皮素对除原虫、产甲烷菌外的瘤胃微生物无抑制作用。

2.3　槲皮素对奶牛机体健康的影响

围产期奶牛采食摄入的能量不足以满足泌乳需要，奶牛动用体脂供能，当肝脏吸收的脂质超过其氧化和分泌时发生脂肪肝[1]。有研究表明，约有50%的奶牛可发生脂肪肝同时伴随肝细胞损害及肝功能下降[61-62]。另外，由于围产期奶牛大量的能量摄入及泌乳造成氧化代谢增强，产生更多活性氧[2-3]。研究发现，槲皮素可减少啮齿动物肝脏脂肪积聚及预防脂肪肝发生[10]。由此，结合槲皮素的保肝作用及抗炎、抗氧化作用，一些学者对槲皮素在奶牛上的作用进行了初步研究。连续28 d通过十二指肠瘘管添加36 mg/kg BW的槲皮素对奶牛超氧化物歧化酶、谷胱甘肽过氧化物酶和过氧化氢酶活性均无显著影响[63]。原因可能在于以下2点：1)槲皮素添加剂量少，添加100 mg/kg BW的槲皮素在mRNA水平上显著提高了奶牛超氧化物歧化酶表达量[64]；2)槲皮素的抗氧化作用与机体健康程度有关，槲皮素对链霉素诱导的糖尿病、人造肝脏损伤有积极作用[65-67]，而对健康小鼠超氧化物歧化酶和过氧化氢酶活性无影响[68]。

槲皮素可提高血液中胰岛素含量，降低葡萄糖含量，与在人糖尿病中的作用一致[69]。但是对于糖代谢相关基因（葡萄糖6磷酸酶、丙酮酸羧化酶和磷酸烯醇式丙酮酸羧化酶）则无显著影响。有报道表明，槲皮素可抑制肠细胞对葡萄糖的吸收而提高肌细胞的吸收[70-71]。因此槲皮素可能通过促进胰岛素的分泌及其他组织对葡萄糖的吸收降低血液葡萄糖含量。

重度脂肪浸润可导致肝细胞破坏，随后引起胞浆天冬氨酸转氨酶释放[69]。谷氨酸脱氢酶主要存在于肝脏中，其血液中含量升高暗示肝细胞死亡或亚致死损伤[72]。有研究表明，槲皮素可显著降低奶牛血液中天冬氨酸转氨酶含量，虽然血液中谷氨酸脱氢酶含量统计学上变化不显著，但是未添加槲皮素奶牛分娩后比分娩前谷氨酸脱氢酶含量增加了 300%，而添加槲皮素奶牛仅增加了 50%[73]。此结果表明，槲皮素具有减少肝损害的作用。另外，槲皮素具有减少肝脏脂肪含量的趋势[64]。因此，槲皮素可能通过减少肝细胞损害，保护肝细胞的正常功能而减少肝脏脂肪含量。

2.4 槲皮素对奶牛生产性能及蹄部健康的影响

饲粮中添加槲皮素可提高泌乳中期奶牛的乳蛋白含量，但对乳脂、乳糖含量无影响[63]。作者认为这可能与槲皮素增加血液中胰岛素含量有关。有研究表明，静脉灌注胰岛素可提高奶牛乳蛋白含量[74]。而在奶牛瘤胃中长期灌注芦丁（槲皮素糖苷衍生物），可使奶牛产奶量提高 10.06%，但对乳品质无显著影响[75]。

MMP 主要功能是降解细胞外基质和基膜，奶牛蹄组织中存在 MMP，在健康状况下，*MMP* 基因的表达及活性均受到严格的调控，但在亚急性瘤胃酸中毒条件下，奶牛蹄组织中 MMP-2 和 MMP-9 的活性上调，进而催化降解基膜等重要结构，使蹄叶组织失去正常的连接、渗透与屏障功能，最终导致真皮小叶与角小叶发生渗出性炎症，形成蹄叶炎[76]。槲皮素抗肿瘤作用中显示，槲皮素可抑制 MMP-2 和 MMP-9 上游通路，阻止其分泌并抑制其活性。因此，槲皮素可能具有预防蹄叶炎的作用。但在奶牛上的研究发现，槲皮素对 *MMP*-2 和 *MMP*-9 表达无显著影响，仅对奶牛蹄白线分离有改善作用[77]。原因可能是，槲皮素对 MMP-2 和 MMP-9 抑制基本为离体试验，而奶牛上的研究中槲皮素添加形式为口服，槲皮素可能被瘤胃微生物降解造成生物利用率低。因此未来有必要开展蹄组织体外培养的研究以确定槲皮素是否具有预防蹄叶炎的作用，以期为研究有效的过瘤胃槲皮素奠定基础。

3 小 结

槲皮素是黄酮类化合物中一种天然植物提取物，具有抗炎、抗氧化及抗肿瘤等功能。槲皮素在奶牛生产上的研究还处于初步阶段，对抑制甲烷产生、减少肝脏脂肪积聚、减少肝损伤、提高乳蛋白含量及预防蹄叶炎方面体现出较大潜力。但是由于槲皮素可被瘤胃微生物降解且上述试验试验动物偏少，因此开发过瘤胃形式槲皮素、开展大规模动物试验进一步研究验证槲皮素在奶牛生产上的作用很有必要。

参考文献：

[1] GROSS J J,SCHWARZ F J,EDER K,et al.Liver fat content and lipid metabolism in dairy cows during early lactation and during a mid-lactation feed restriction[J].Journal of Dairy Science,2013,96(8):5008–5017.

[2] SORDILLO L M,O’BOYLE N,GANDY J C,et al.Shifts in thioredoxin reductase activity and oxidant status in mononuclear cells obtained from transition dairy cattle[J].Journal of Dairy Science,2007,90(3):1186–1192.

[3] CELI P.Biomarkers of oxidative stress in ruminant medicine[J].Immunopharacology and Immunotoxicology,2011,33(2):233–240.

[4] LEMERLE C,GODDARD M E.Assessment of heat stress in dairy cattle in papua new guinea[J].Tropical Animal Health and Production,1986,18(4):232–242.
[5] 宋小珍,付戴波,瞿明仁,等.热应激对肉牛血清内分泌激素含量、抗氧化酶活性及生理生化指标的影响[J].动物营养学报,2012,24(12):2485–2490.
[6] WEST J W.Effects of heat-stress on production in dairy cattle[J].Journal of Dairy Science,2003,86(6):2131–2144.
[7] 李建国,桑润滋,张正珊,等.热应激对奶牛生理常值、血液生化指标、繁殖及泌乳性能的影响[J].河北农业大学学报,1998(4):69-75.
[8] GWAZDAUSKAS F C.Effects of climate on reproduction in cattle[J].Journal of Dairy Science,1985,68(6):1568–1578.
[9] JOVEN J,ESPINEL E,RULL A,et al.Plant-derived polyphenols regulate expression of miRNA paralogs miR-103/107 and miR-122 and prevent diet-induced fatty liver disease in hyperlipidemic mice[J].Biochimica et Biophysica Acta (BBA)-General Subjects,2012,1820(7):894–899.
[10] AGUIRRE L,ARIAS N,MACARULLA M T,et al.Beneficial effects of quercetin on obesity and diabetes[J].The Open Nutraceuticals Journal,2011,4(1):189–198.
[11] CUI Y M,HAN Y,YANG X B,et al.Protective effects of quercetin and quercetin-5',8-disulfonate against carbon tetrachloride-caused oxidative liver injury in mice[J].Molecules,2014,19(1):291–305.
[12] RATHEE P,CHAUDHARY H,RATHEE S,et al.Mechanism of action of flavonoids as anti-inflammatory agents:a review[J].Inflammation & Allergy-Drug Targets,2009,8(3):229–235.
[13] 吴亚楠,赵鹏翔,马雪梅.NF-κB 研究进展及其与炎症的关系[J].安徽农业科学,2012,40(34):16533–16535,16601.
[14] CHO S Y,PARK S J,KWON M J,et al.Quercetin suppresses proinflammatory cytokines production through MAP kinases and NF-κB pathway in lipopolysaccharide-stimulated macrophage[J].Molecular and Cellular Biochemistry,2003,243(1/2):153–160.
[15] MIN Y D,CHOI C H,BARK H,et al.Quercetin inhibits expression of inflammatory cytokines through attenuation of NF-κB and p38 MAPK in HMC-1 human mast cell line[J].Inflammation Research,2007,56(5):210–215.
[16] TRIBOLO S,LODI F,CONNOR C,et al.Comparative effects of quercetin and its predominant human metabolites on adhesion molecule expression in activated human vascular endothelial cells[J].Atherosclerosis,2008,197(1):50–56.
[17] KOBUCHI H,ROY S,SEN C K,et al.Quercetin inhibits inducible ICAM-1 expression in human endothelial cells through the JNK pathway[J].American Journal of Physiology-Cell Physiology,1999,277(3):C403-C411.
[18] BANERJEE T,VAN DER VLIET A,ZIBOH V A.Downregulation of COX-2 and iNOS by amentoflavone and quercetin in A549 human lung adenocarcinoma cell line[J].Prostaglandins,Leukotrienes and Essential Fatty Acids,2002,66(5/6):485–492.
[19] O'LEARY K A,DE PASCUAL-TEREASA S,NEEDS P W,et al.Effect of flavonoids and vitamin E on cyclooxygenase-2 (COX-2) transcription[J].Mutation Research,2004,551(1/2):245–254.
[20] RASO G M,MELI R,DI CARLO G,et al.Inhibition of inducible nitric oxide synthase and cyclooxygenase-2 expression by flavonoids in macrophage J774A.1[J].Life

Sciences,2001,68(8):921–931.
[21] GARCÍA-MEDIAVILLA V,CRESPO I,COLLADO P S,et al.The anti-inflammatory flavones quercetin and kaempferol cause inhibition of inducible nitric oxide synthase,cyclooxygenase-2 and reactive C-protein,and down-regulation of the nuclear factor kappaB pathway in chang liver cells[J].European Journal of Pharmacology,2007,557(2/3):221–229.
[22] KEMPURAJ D,CASTELLANI M L,PETRARCA C,et al.Inhibitory effect of quercetin on tryptase and interleukin-6 release,and histidine decarboxylase mRNA transcription by human mast cell-1 cell line[J].Clinical and Experimental Medicine,2006,6(4):150–156.
[23] PARK H H,LEE S Y,SON H Y,et al.Flavonoids inhibit histamine release and expression of proinflammatory cytokines in mast cells[J].Archives of Pharmacal Research,2008,31(10):1303–1311.
[24] BLACKBURN W D,HECK L W,WALLACE R W.The bioflavonoid quercetin inhibits neutrophil degranulation,superoxide production,and the phosphorylation of specific neutrophil proteins[J].Biochemical and Biophysical Research Communications,1987,144(3):1229–1236.
[25] NIJVELDT R J,VAN NOOD E,VAN HOORN D E,et al.Flavonoids:a review of probable mechanisms of action and potential applications[J].The American Journal of Clinical Nutrition,2001,74(4):418–425.
[26] UENO I,KOHNO M,HARAIKAWA K,et al.Interaction between quercetin and superoxide radicals.Reduction of the quercetin mutagenicity[J].Journal of Pharmacobio-Dynamics,1984,7(11):798–803.
[27] LIN C M,CHEN C S,CHEN C T,et al.Molecular modeling of flavonoids that inhibits xanthine oxidase[J].Biochemical and Biophysical Research Communications,2002,294(1):167–172.
[28] RATTY A K,DAS N P.Effects of flavonoids on nonenzymatic lipid peroxidation:structure-activity relationship[J].Biochemical Medicine and Metabolic Biology,1988,39(1):69–79.
[29] COSKUN O,KANTER M,KORKMAZ A,et al.Quercetin,a flavonoid antioxidant,prevents and protects streptozotocin-induced oxidative stress and β-cell damage in rat pancreas[J].Pharmacological Research,2005,51(2):117–123.
[30] YOSHIDA M,SAKAI T,HOSOKAWA N,et al.The effect of quercetin on cell cycle progression and growth of human gastric cancer cells[J].FEBS Letters,1990,260(1):10–13.
[31] HOSOKAWA N,HIRAYOSHI K,NAKAI A,et al.Flavonoids inhibit the expression of heat shock proteins[J].Cell Structure and Function,1990,15(6):393–401.
[32] HUANG Y T,HWANG J J,LEE P P,et al.Effects of luteolin and quercetin,inhibitors of tyrosine kinase,on cell growth and metastasis - associated properties in A431 cells overexpressing epidermal growth factor receptor[J].British Journal of Pharmacology,1999,128(5):999–1010.
[33] CASTILLO M H,PERKINS E,CAMPBELL J H,et al.The effects of the bioflavonoid quercetin on squamous cell carcinoma of head and neck origin[J].The American Journal of Surgery,1989,158(4):351–355.
[34] KANDASWAMI C,PERKINS E,SOLONIUK D S,et al.Antitproliferative effects of citrus

flavonoids on a human squamous cell carcinoma *in vitro*[J].Cancer Letters,1991,56(2):147–152.
[35] SCAMBIA G,RANELLETTI F O,PANICI P B,et al.Inhibitory effect of quercetin on OVCA 433 cells and presence of type Ⅱ oestrogen binding sites in primary ovarian tumours and cultured cells[J].British Journal of Cancer,1990,62(6):942–946.
[36] LEE L T,HUANG Y T,HWANG J J,et al.Transinactivation of the epidermal growth factor receptor tyrosine kinase and focal adhesion kinase phosphorylation by dietary flavonoids:effect on invasive potential of human carcinoma cells[J].Biochemical Pharmacology,2004,67(11):2103–2114.
[37] SUOLINNA E M,BUCHSBAUM R N,RACKER E.The effect of flavonoids on aerobic glycolysis and growth of tumor cells[J].Cancer Research,1975,35(7):1865–1872.
[38] 李敏,林俊.细胞凋亡途径及其机制[J].国际妇产科学杂志,2014,41(2):103–107.
[39] PRIMIKYRI A,CHATZIATHANASIADOU M V,KARALI E,et al.Direct binding of Bcl-2 family proteins by quercetin triggers its pro-apoptotic activity[J].ACS Chemical Biology,2014,9(12):2737–2741.
[40] DUO J,YING G G,WANG G W,et al.Quercetin inhibits human breast cancer cell proliferation and induces apoptosis via Bcl-2 and Bax regulation[J].Molecular Medicine Reports,2012,5(6):1453–1456.
[41] CHENG S P,GAO N,ZHANG Z,et al.Quercetin induces tumor-selective apoptosis through down-regulation of Mcl-1 and activation of bax[J].Clinical Cancer Research,2010,16(23):5679–5691.
[42] KUHAR M,SEN S,SINGH N.Role of mitochondria in quercetin-enhanced chemotherapeutic response in human non-small cell lung carcinoma H-520 cells[J].Anticancer Research,2006,26(2A):1297–1303.
[43] NGUYEN T T T,TRAN E,NGUYEN T H,et al.The role of activated MEK-ERK pathway in quercetin-induced growth inhibition and apoptosis in A549 lung cancer cells[J].Carcinogenesis,2004,25(5):647–659.
[44] PRIYADARSINI R V,MURUGAN R S,MAITREYI S,et al.The flavonoid quercetin induces cell cycle arrest and mitochondria-mediated apoptosis in human cervical cancer (HeLa) cells through p53 induction and NF-κB inhibition[J].European Journal of Pharmacology,2010,649(1/2/3):84–91.
[45] CHIEN S Y,WU Y C,CHUNG J G,et al.Quercetin-induced apoptosis acts through mitochondrial-and caspase-3-dependent pathways in human breast cancer MDA-MB-231 cells[J].Human & Experimental Toxicology,2009,28(8):493–503.
[46] PEREZ-VIZCAINO F,BISHOP-BAILLEY D,LODI F,et al.The flavonoid quercetin induces apoptosis and inhibits JNK activation in intimal vascular smooth muscle cells[J].Biochemical and Biophysical Research Communications,2006,346(3):919–925.
[47] SUN Z J,CHEN G,HU X,et al.Activation of PI3K/Akt/IKK-α/NF-κB signaling pathway is required for the apoptosis-evasion in human salivary adenoid cystic carcinoma:its inhibition by quercetin[J].Apoptosis,2010,15(7):850–863.
[48] ZHANG X M,HUANG S P,XU Q.Quercetin inhibits the invasion of murine melanoma B16-BL6 cells by decreasing pro-MMP-9 via the PKC pathway[J].Cancer Chemotherapy and Pharmacology,2004,53(1):82–88.
[49] ENDE C,GEBHARDT R.Inhibition of matrix metalloproteinase-2 and -9 activities by

selected flavonoids[J].Planta Medica,2004,70(10):1006–1008.
[50] 冯仰廉.反刍动物营养学[M].北京:科学出版社,2004.
[51] BERGER L M,WEIN S,BLANK R,et al.Bioavailability of the flavonol quercetin in cows after intraruminal application of quercetin aglycone and rutin[J].Journal of Dairy Science,2012,95(9):5047–5055.
[52] BERGER L M,BLANK R,ZORN F,et al.Ruminal degradation of quercetin and its influence on fermentation in ruminants[J].Journal of Dairy Science,2015,98(8):5688–5698.
[53] GOHLKE A,INGELMANN C J,NÜRNBERG G,et al.Bioavailability of quercetin from its aglycone and its glucorhamnoside rutin in lactating dairy cows after intraduodenal administration[J].Journal of Dairy Science,2013,96(4):2303–2313.
[54] SHU Y,LIU Y,LI L,et al.Antibacterial activity of quercetin on oral infectious pathogens[J].African Journal of Microbiology Research,2011,5(30):5358–5361.
[55] ANNISON E F,ARMSTRONG D G.Volatile fatty acid metabolism and energy supply[M]//PHILLIPSON A T.Physiology of Digestion and Metabolism in the Ruminant.Newcastle Upon Tyne:Oriel Press,1970.
[56] LOURENÇO M,CARDOZO P W,CALSAMIGLIA S,et al.Effects of saponins,quercetin,eugenol,and cinnamaldehyde on fatty acid biohydrogenation of forage polyunsaturated fatty acids in dual-flow continuous culture fermenters[J].Journal of Animal Science,2008,86(11):3045–3053.
[57] OSKOUEIAN E,ABDULLAH N,OSKOUEIAN A.Effects of flavonoids on rumen fermentation activity,methane production,and microbial population[J].BioMed Research International,2013,2013:349129.
[58] KAMRA D N,PAWAR M,SINGH B.Effect of plant secondary metabolites on rumen methanogens and methane emissions by ruminants[M]//PATRA A K.Dietary Phytochemicals and Microbes.Netherlands:Springer,2012:351–370.
[59] ADER P,WESSMANN A,WOLFFRAM S.Bioavailability and metabolism of the flavonol quercetin in the pig[J].Free Radical Biology and Medicine,2000,28(7):1056–1067.
[60] LEIBER F,KUNZ C,KREUZER M.Influence of different morphological parts of buckwheat (*Fagopyrum esculentum*) and its major secondary metabolite rutin on rumen fermentation *in vitro*[J].Czech Journal of Animal Science,2012,57(1):10–18.
[61] BOBE G,YOUNG J W,BEITZ D C.*Invited review*:pathology,etiology,prevention,and treatment of fatty liver in dairy cows[J].Journal of Dairy Science,2004,87(10):3105–3124.
[62] ESPOSITO G,IRONS P C,WEBB E C,et al.Interactions between negative energy balance,metabolic diseases,uterine health and immune response in transition dairy cows[J].Animal Reproduction Science,2014,144(3/4):60–71.
[63] GOHLKE A, INGELMANN C J, NÜRNBERG G,et al.Influence of 4-week intraduodenal supplementation of quercetin on performance,glucose metabolism,and mRNA abundance of genes related to glucose metabolism and antioxidative status in dairy cows[J].Journal of Dairy Science,2013,96(11):6986–7000.
[64] STOLDT A K,MIELENZ M,NÜRNBERG G,et al.Effects of a six-week intraduodenal supplementation with quercetin on liver lipid metabolism and oxidative stress in peripartal dairy cows[J].Journal of Animal Science,2016,94(5):1913–1923.
[65] JEONG S M,KANG M J,CHOI H N,et al.Quercetin ameliorates hyperglycemia and dyslipidemia and improves antioxidant status in type 2 diabetic db/db mice[J].Nutrition

Research and Practice,2012,6(3):201–207.
[66] MOLINA M F,SANCHEZ-REUS I,IGLESIAS I,et al.Quercetin,a flavonoid antioxidant,prevents and protects against ethanol-induced oxidative stress in mouse liver[J].Biological & Pharmaceutical Bulletin,2003,26(10):1398–1402.
[67] SANCHETI S,SANCHETI S,BAFNA M,et al.Evaluation of antidiabetic,antihyperlipidemic and antioxidant effects of *Boehmeria nivea* (L.) Gaudich.,Urticaceae,root extract in streptozotocin-induced diabetic rats[J].Revista Brasileira de Farmacognosia,2011,21(1):146–154.
[68] IGARASHI K,OHMUMA M.Effects of isorhamnetin,rhamnetin,and quercetin on the concentrations of cholesterol and lipoperoxide in the serum and liver and on the blood and liver antioxidative enzyme activities of rats[J].Bioscience,Biotechnology,and Biochemistry,1995,59(4):595–601.
[69] LIU P,HE B X,YANG X L,et al.Activities of aspartate aminotransferase,alanine aminotransferase,gamma-glutamyltransferase,alkaline phosphatase in plasma of postpartum holstein cows[J].Journal of Animal and Veterinary Advances,2012,11(8):1270–1274.
[70] CERMAK R,LANDGRAF S,WOLFFRAM S.Quercetin glucosides inhibit glucose uptake into brush-border-membrane vesicles of porcine jejunum[J].British Journal of Nutrition,2004,91(6):849–855.
[71] EID H M,MARTINEAU L C,SALEEM A,et al.Stimulation of AMP-activated protein kinase and enhancement of basal glucose uptake in muscle cells by quercetin and quercetin glycosides,active principles of the antidiabetic medicinal plant *Vaccinium vitis-idaea*[J].Molecular Nutrition & Food Research,2010,54(7):991–1003.
[72] OK M,ŞEN I,GÜZELBEKTEŞ H,et al.The importance of concentrations of sorbitol dehydrogenase and glutamate dehydrogenase and B-mode ultrasonographic examination in the diagnosis of hepatic lipidosis in dairy cows[J].Kafkas Üniversitesi Veteriner Fakültesi Dergisi,2013,19(Suppl.A):A117–A123.
[73] STOLDT A K,DERNO M,NÜRNBERG G,et al.Effects of a 6-wk intraduodenal supplementation with quercetin on energy metabolism and indicators of liver damage in periparturient dairy cows[J].Journal of Dairy Science,2015,98(7):4509–4520.
[74] MOLENTO C F M,BLOCK E,CUE R I,et al.Effects of insulin,recombinant bovine somatotropin,and their interaction on insulin-like growth factor-Ⅰ secretion and milk protein production in dairy cows[J].Journal of Dairy Science,2002,85(4):738–747.
[75] CUI K,GUO X D,TU Y,et al.Effect of dietary supplementation of rutin on lactation performance,ruminal fermentation and metabolism in dairy cows[J].Journal of Animal Physiology and Animal Nutrition,2015,99(6):1065–1073.
[76] SHEARER J K.Nutritional and animal welfare implications to lameness[C]//Tri-state dairy nutrition conference.Fort Wayne:[s.n.],2010.
[77] PIERSON M L.The use of natural plant extracts as a feed additive to prevent laminitis in lactating dairy cows[D].Master’s Thesis.Eugene:Oregon State University,2007.

Quercetin: Pharmacological Action Mechanism and Application in Dairy Cows Production

GUO Changzheng FENG Panfei MAO Shengyong*

*Corresponding author, professor, E-mail： maoshengyong@163.com

（责任编辑 王智航）

（*Jiangsu Key Laboratory of Gastrointestinal Nutrition and Animal Health, Laboratory of Gastrointestinal Microbiology, Nanjing Agricultural University, Nanjing* 210095, *China*）

Abstract： Quercetin is a common flavonoid in herbs, fruits and vegetables, and has anti-inflammatory, antibacterial, antioxidant, anti-tumor and anti-cancer and other pharmacological activities. In recent years, studies found that quercetin addition could improve rumen fermentation of dairy cows, and could affect glucose metabolism and lipid metabolism. In this paper, the pharmacological mechanism of quercetin and its application in dairy cows production were reviewed to provide reference for the further development and application.

Key words： quercetin; biochemical function; mechanism; dairy cow